Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
June 4th, 2015

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committees discussed new drug application (NDA) 022526, flibanserin 100 milligram (mg) tablets, submitted by Sprout Pharmaceuticals Inc., proposed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

These summary minutes for the June 4th, 2015, joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on July 24, 2015.

I certify that I attended the June 4th, 2015, joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflects what transpired.

/s/
Kalyani Bhatt
Designated Federal Officer, BRUDAC

/s/
Vivian Lewis, MD
Acting Chairperson, BRUDAC

Summary Minutes of the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee June 4, 2015

The following is the final report of the joint meeting of the joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on June 4, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Bone, Reproductive and Urologic Products and the Office of Surveillance and Epidemiology and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm446101.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on June 4, 2015 at the FDA White Oak Campus, Building 31, the Great Room (Rm. 1503) White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided background materials from the FDA and Sprout Pharmaceuticals, Inc. The meeting was called to order by Vivian Lewis, MD (Acting Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 375 persons in attendance. There were 37 Open Public Hearing (OPH) speaker presentations with a total of 42 speakers.

Issue: The committees discussed new drug application (NDA) 022526, flibanserin 100 milligram (mg) tablets, submitted by Sprout Pharmaceuticals Inc., proposed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Attendance:
Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Kathryn M. Curtis, PhD; Vivian Lewis (*Acting Chairperson*), MD; Amy Whitaker, MD, MS

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Non-Voting): Keith Gordon, MD (*Industry Representative)*

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Toby Chai, MD; Jennifer Dietrich, MD; Amy H. Herring, ScD; Stuart S. Howards, MD; Julia V. Johnson, MD *(Chairperson)*; Clifford J. Rosen, MD

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Tobias Gerhard, PhD, RPh; Jeanmarie Perrone, MD, FACMT; Marjorie Shaw Phillips, MS, RPh, FASHP; Til Stürmer, MD, MPH, PhD

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Almut Winterstein, PhD *(Chairperson)*; Niteesh K. Choudhry, MD, PhD; Karen M. Hopkins, MD *(Consumer Representative)*; Andy S. Stergachis, PhD, RPh; Linda S. Tyler, PharmD, FASHP

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Patricia Cavazzoni, MD *(Industry Representative)*

Temporary Members (Voting): G. Caleb Alexander, MD, MS; Diane D. Aronson *(Patient Representative)*; Emilia Bagiella, PhD; Elizabeth Bell-Perkins, MPH *(Acting Consumer Representative)*; Kelly Besco, PharmD, FISMP, CPPS; Marianne Brandon PhD, IF; Kathryn E. Flynn, PhD; Walid Gellad, MD, MPH; Marsha K. Guess, MD, MS; Philip Hanno, MD, MPH; Julia R. Heiman, PhD; Crista Johnson-Agbakwu, MD, MSc, FACOG; Lorenzo Leggio, MD, PhD, MSc.; A. Michael Lincoff, MD; Michelle Orza, ScD *(Acting Consumer Representative)*; Robert Silbergleit, MD; Kevin Weinfurt, PhD

FDA Participants (Non-Voting):
Julie Beitz, MD; Hylton Joffe, MD, MMSc; Christine Nguyen, MD; Christina Chang, MD, MPH; Olivia Easley, MD; Catherine Sewall, MD, MPH; LaiMing Lee, PhD; Claudia Manzo, MD; Kim Lehrfeld, PharmD, BCPS

Designated Federal Officer: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Lisa Larkin, MD, FACP, NCMP (UC Health Women's Center) ; Irwin Goldstein, MD, IF and Sue W. Goldstein, CCRC, IF (San Diego Sexual Medicine); Sally Greenberg (Executive Director, National Consumers League); Lori Weinstein, (CEO/Executive Director, Jewish Women International); Susan Scanlan (Chair, Even the Score); Michael L Krychman, MD, MPH (Executive Director, Southern California Center for Sexual Health and Survivorship Medicine, Inc); Wayne C. Shields (President and CEO, Association of Reproductive Health Professional); Anita H. Clayton, MD (Professor and Interim Chair, University of Virginia Department of Psychiatry & Neurobehavioral Sciences); Beth Battaglino, RN (CEO & President, HealthyWomen); Amanda and Ben Parrish; Katherine Campbell; Lynn Barclay (President & CEO, Health Policy, American Sexual Health Association); Judith Reid-Haff; Barbara Gattuso and Vicki Lofthus; Gregg Gattuso; Gay Johnson (CEO, National Association of Nurse Practitioners in Women's Health); Kelli Stoup; Cindy Pearson (Program Director, National Women's Health Network); Lauren F. Streicher, MD (Clinical Associate Professor of Obstetrics and Gynecology, Feinberg School of Medicine Northwestern University); Alessandra Hirsch and Adriane Fugh-Berman, MD (Georgetown University Medical Center/PharmOut); Sidney M. Wolfe, MD (Founder, Senior Advisor, Health Research Group of Public Citizen); Christina Silcox (Senior Fellow, National Center for Health Research); Derek Haff; Alyse Kelly-Jones, MD (Mintview Women's Care); Maureen Whelihan, MD (Center For Sexual Health and Education); Ashley H. Tapscott, DO (Carolina Urology Partners); Erica Palim; Julianne Adams Birt, MD, FACOG (President, Radiant Women's Heath; Chief, Department of Women's Services, Rockdale Medical Center); Karen M. Hicks; Leonore Tiefer, PhD (The New View Campaign); Jan Erickson (Director of Government Relations, National Organization for Women); Liz Canner (Director Astrea Media, Inc.); James A. Simon, MD,

CCD, NCMP, IF, FACOG (Clinical Professor, George Washington University; President and Medical Director, Women's Health & Research Consultants®); Beverly J. Wiesen (Apex Executive Search, LLC); Marta Hill Gray (Red Hot Mammas); Sharon J. Parish, MD, IF, NCMP (Professor of Medicine in Clinical Psychiatry & Professor of Clinical Medicine, Weill Cornell Medical College; President, International Society for the Study of Women's Sexual Health); Vikki Pedigo, MSN, WHNP-BC and Brooke Faught, MSN, WHNP-BC, IF (Nurse Practitioner/Clinical Director, Women's Institute for Sexual Health)

The agenda proceeded as follows:

7:30 a.m.	Call to Order and Introduction of Committee	**Vivian Lewis, MD** (Acting Chairperson), BRUDAC
	Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
7:40 a.m.	FDA Opening Remarks	**Hylton V. Joffe, MD, MMSc** Director Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
7:55 a.m.	**INDUSTRY PRESENTATIONS**	Sprout Pharmaceuticals, Inc.
	Flibanserin Overview	**Josephine Torrente, MS, JD** Executive Vice President of Corporate and Regulatory Affairs Sprout Pharmaceuticals, Inc.
	Overview and Impact of HSDD	**Sheryl Kingsberg, PhD** Chief, Division of Behavioral Medicine Department of Obstetrics and Gynecology MacDonald Women's Hospital University Hospitals Case Medical Center Professor Departments of Reproductive Biology and Psychiatry Case Western Reserve University School of Medicine
	HSDD Endpoints	**Ray Rosen, PhD** Chief Scientist New England Research Institutes
	Efficacy	**David Portman, MD** Director, Columbus Center for Women's Health Research Adjunct Instructor Department of Obstetrics and Gynecology Ohio State University

INDUSTRY PRESENTATIONS (CONT.)

	Safety	**Stuart Apfel, MD** Vice President of Clinical Safety Sprout Pharmaceuticals, Inc.
	Risk Management	**Josephine Torrente, MS, JD**
	Clinical Considerations	**David Portman, MD**
9:05 a.m.	Clarifying Questions to Industry	
9:35 a.m.	**BREAK**	
9:45 a.m.	**FDA PRESENTATIONS**	
	Outcome Assessments	**Ashley Slagle, MS, PhD** Endpoints Reviewer Clinical Outcome Assessments Staff OND, CDER, FDA
	Efficacy	**Catherine Sewell, MD, MPH** Medical Officer DBRUP, ODE III, OND, CDER, FDA
	Increased Flibanserin Exposure by Intrinsic and Extrinsic Factors	**LaiMing Lee, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology III Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS) CDER, FDA
	Safety	**Olivia Easley, MD** Medical Officer DBRUP, ODE III, OND, CDER, FDA
	Risk Management Options for Flibanserin	**Kimberly Lehrfeld, PharmD** Team Leader Division of Risk Management (DRISK) Office of Medication Error Prevention and Analysis Office of Surveillance and Epidemiology (OSE) CDER, FDA
	FDA PRESENTATIONS (CONT.)	
	Summary Remarks	**Christina Chang, MD, MPH** Clinical Team Leader DBRUP, ODE III, OND, CDER, FDA
10:55 a.m.	Clarifying Questions to FDA	

11:25 a.m. **LUNCH**

12:25 p.m. Open Public Hearing (OPH)

2:10 p.m. Clarifying Questions

2:30 p.m. Questions to the Committee/Committee Discussion

3:00 p.m. **BREAK**

3:10 p.m. Questions to the Committee/Committee Discussion (cont.)

5:30 p.m. **ADJOURNMENT**

Questions to the Committee:

1. **DISCUSSION:** Comment on the clinical significance of the observed placebo-corrected treatment effects of flibanserin on satisfying sexual events, sexual desire, and related distress.

   Committee Discussion: *The responder analysis that assessed clinical meaningfulness was noted to be an important consideration of clinical benefit; these data showed a placebo-corrected difference of about 10 percent. In general, the observed placebo-corrected treatment effects were noted to be numerically small with sizeable placebo responses across all three key efficacy endpoints. It was noted that a substantial proportion of patients would still carry a diagnosis of HSDD despite improvement with flibanserin. Nonetheless the placebo-corrected effects were considered clinically significant and meaningful, particularly for the 10 percent of responders.*

   Please see the transcript for details of the committee's discussion.

2. **DISCUSSION:** Take into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin, if approved. Then, discuss your level of concern with the risks of hypotension and syncope when flibanserin is used alone and when flibanserin is used with alcohol.

   Include a discussion of the following:

   a. Whether the alcohol interaction study conducted mostly in men who were moderate alcohol drinkers adequately assesses risk in premenopausal women and in those who generally drink less alcohol than moderate drinkers

   b. The feasibility of avoiding alcohol indefinitely while using flibanserin, taking into account the prevalence of alcohol use in the United States

c. Whether alcohol use should be contraindicated in patients using flibanserin

d. Whether a risk evaluation and mitigation strategy (REMS) is necessary and would be able to ensure that the benefits outweigh the risks of hypotension and syncope with flibanserin alone and with concomitant use of alcohol

e. If a REMS is appropriate, comment on whether the Applicant's proposed REMS (consisting of a Medication Guide and communication plan) is sufficient to ensure safe use or whether additional elements such as elements to assure safe use (ETASU) with pharmacy certification or ETASU with pharmacy and provider certification, are needed.

Committee Discussion: *Committee members noted that the safety concerns could be magnified in the population who would use flibanserin, if approved, given the likelihood for use beyond the narrowly defined population enrolled in the clinical trials, including use among postmenopausal women.*

Several committee members emphasized that syncope and somnolence are not necessarily benign because these adverse events could lead to life-threatening consequences, such as accidental injuries and traffic accidents. It was noted that these consequences may be difficult to capture in the postmarketing setting.

There was strong consensus among the committee members that the alcohol study presented by the Applicant was inadequate to assess risk in women because of the overwhelming preponderance of men enrolled in the study.

Most committee members were concerned that the "worse-case scenario" related to alcohol use in women had not been established, citing the inadequate alcohol study, and the lack of prospective information on alcohol use in the Phase 3 trials. However, some members felt reassured by the data collected during the Phase 3 trials, because patients who reported being social drinkers and moderate drinkers were not excluded from the clinical program. Some committee members recommended that alcohol use should be contraindicated in patients using flibanserin, others stated that a contraindication may be too strong based on the Phase 3 data. Others felt that there were insufficient data on which to base their recommendation.

Comments with regard to a REMS included the need for prescriber certification and ensuring healthcare providers and patients are well-informed about the risks. Some expressed uncertainty about the effectiveness of REMS.

Please see the transcript for details of the committee's discussion.

3. **DISCUSSION:** Take into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin, if approved. Then, discuss your level of concern with any other safety findings.

Committee Discussion: *Many committee members commented that there were other safety issues of concern. These included generalizability of existing clinical data to patients with co-morbidities or taking concomitant medications (e.g., benzodiazepines), potential off-label use (e.g., in postmenopausal women), pregnancy outcomes (unintended pregnancies may occur given the indicated patient population), interaction with the numerous and prevalent CYP3A4 inhibitors, uncertainty of the clinical risk for breast cancer, potential interactions with over-the-counter medications and dietary supplements. Some members commented that additional long term safety data are needed because this drug would be administered chronically.*

Please see the transcript for details of the committee's discussion.

4. **VOTE:** Is the overall benefit/risk profile of flibanserin acceptable to support approval for hypoactive sexual desire disorder (HSDD) in premenopausal women?

   A. Yes, with labeling alone to manage the risks

   B. Yes, but only if certain risk management options beyond labeling are implemented

   C. No

   Please provide a rationale for your vote. If you voted for B, describe the risk management option(s) that must be implemented in addition to labeling to ensure that the benefits outweigh the risks. If you voted for C, describe what additional data are needed to ensure a positive benefit/risk profile.

Vote: A) 0 B) Yes: 18 C) No: 6 Abstain: 0

Committee Discussion: *Six of the 24 voting committee members voted against approval. Rationale for the no votes included the marginal efficacy as well as the significant safety concerns, particularly the alcohol interaction, that outweighed potential benefits.*

The remaining 18 voting committee members voted that the overall benefit/risk profile of flibanserin is acceptable to support approval for HSDD in premenopausal women but only if certain risk mitigation strategies beyond labeling are implemented. These members also noted the marginal efficacy and significant safety concerns but took into account the unmet medical need. There was strong support for an ETASU REMS, with prescriber and pharmacy certification, although some committee members were concerned that this may limit access to treatment. There were some comments about incorporating informed consent to ensure patients document that they understand the benefits and risks of treatment. Several members supported limited marketing to avoid use in patients who may be inappropriate or too dissimilar to the trial population.

Please see the transcript for details of the committee's discussion.

The meeting was adjourned at approximately 5:00 pm.